REMARKS

Claims 41-44 and 46-65 are pending in this application. Claims 1-40 and 45 have been cancelled without prejudice or disclaimer. Claims 41-44 and 46-53 have been amended. Claims 54-64 have been withdrawn as drawn to a non-elected subject matter. Claim 65 has been newly added.

Applicants, by canceling or amending any claims, make no admission as to the validity of any rejection made by the Examiner against any such claims. Applicants reserve the right to reassert any of the claims cancelled and/or the original claim scope of any claim amended, in a continuing application.

Claim 41 has been amended to recite the subject matter of cancelled claim 45. Specifically, claim 41 has been amended to recite a "drug delivery system, comprising: a plurality of nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead, the nanoparticles or microparticle being in an amorphous, non-crystalline state which enhances dissolution of the poorly soluble drug upon administration; and a disintegrate mixed with the bead." Support for the amendment to claim 41 can be found throughout the specification and claims as originally filed.

Claims 42-44 and 46-53 have been amended to be placed in proper US form. Support for the amendments to claims 41-44 and 46-53 can be found throughout the specification and claims as originally filed.

Claim 65 has been newly added. New claim 65 is directed to the "drug delivery system according to claim 41, wherein the poorly soluble drug is selected from the group consisting of simvastatine, statines, risperidone, carvedilol, carbamazepine,

oxcarbazepine, zaleplon and galantamine." Support for this amendment can be found throughout the specification and claims as originally filed.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, claims 42-44 and 47 have been rejected under 35 USC § 112, second paragraph.

The Examiner asserts that claims 42-44 and 47 are indefinite for because: (1) in claim 42, the phrase "a single species of a hydrophilic polymer" is allegedly unclear; (2) claims 43-44 allegedly recite improper Markush language;(3) claim 44 allegedly recites both genus and species in the same Markush group; and (4) in claim 47, there is insufficient antecedent basis for a crosslinker.

In view of the following, this rejection is respectfully traversed.

With regard to claim 42, Applicants submit that a person of ordinary skill in the art would fully understand the phrase "a single species of a hydrophilic polymer." In this regard, Applicants submit that the Examiner's interpretation of the phrase is reasonable.

Regarding the Markush language in claims 43-44, Applicants submit that, as amended, claims 43-44 now recite proper Markush language.

With regard to the genus and species recited in claim 44, Applicants submit that as amended claim 44 no longer recites both genus and species in the same Markush group.

Regarding claim 47, Applicants submit that claim 47 has been amended to correct dependency.

Therefore, Applicants submit claims 42-44 and are clear and definite within the meaning of 35 USC § 112. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

II. At page 5 of the Official Action, claims 41-43 and 50 have been provisionally rejected on the grounds of statutory type double patenting over co-pending Application No. 10/590,621 further in view of Stainforth et al. (US Published Application No. 2004/0265374) and Lee (of record).

The Examiner asserts that claims 41-43 and 50 are not patentably distinct from the claims in co-pending Application No. 10/590,621 for the reasons set forth in the Official Action.

Applicants respectfully submit that, as claim 41 has been amended to recite the subject matter of cancelled claim 45, this rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

III. At page 7 of the Official Action, claims 41-43 and 46 have been rejected under 35 USC § 103 as being unpatentable over Cooper et al. (WO 2004/011537) further in view of Lee (of record).

The Examiner asserts that claims 41-43 and 46 are allegedly obvious for the reasons set forth in the Official Action.

Applicants respectfully submit that, as claim 41 has been amended to incorporate the subject matter of non rejected (and now cancelled) claim 45, this rejection has been rendered moot. Therefore, Applicants submit that whether taken alone, or in combination, the cited references do not teach or suggest every element of the pending

claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

IV. At page 8 of the Official Action, claims 41-44 and 46-49 have been rejected under 35 USC § 103 as being unpatentable over Soon-Shiong et al. (US Published Application No. 2002/0090399) further in view of Desai et al (US Published Application No. 2007/0092563).

The Examiner asserts that claims 41-44 and 46-49 are allegedly obvious for the reasons set forth in the Official Action.

Applicants respectfully submit that, as claim 41 has been amended to incorporate the subject matter of non rejected (and now cancelled) claim 45, this rejection has been rendered moot. Therefore, Applicants submit that whether taken alone, or in combination, the cited references do not teach or suggest every element of the pending claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

V. At page 10 of the Official Action, claims 51-53 have been rejected under 35 USC § 103 as being unpatentable over Soon-Shiong et al. further in view of Lee.

The Examiner asserts that claims 51-53 are allegedly obvious for the reasons set forth in the Official Action.

Independent claim 51 is directed to drug delivery system, comprising: an active ingredient dispersed within a crosslinked polymeric bead, the crosslinked polymeric bead being crosslinked by a cation selected from the group consisting of calcium, iron, magnesium and copper, and a disintegrant comprising a chelator of calcium. Claims 52-53 depend, either directly or in directly, from claim 51.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because whether taken alone, or in combination, none of the cited references teach or suggest every element of the presently pending claims as required by In re Wilson. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VI. At page 12 of the Official Action, claims 41-45 and 50 have under 35 USC § 103 as being unpatentable over Desai et al. further in view of Catron et al. (US Patent No. 6,146,671).

The Examiner asserts that it would have been obvious use the gelatin beads described by Catron et al. with the system described by Desai et al.

In view of the following, the rejection of claims 41-44 and 50 is respectfully traversed.

Applicants note that claim 45 has been cancelled without prejudice or disclaimer. Therefore the rejection of claim 45 has been rendered moot.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a

reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because whether taken alone, or in combination, none of the cited references teach or suggest every element of the presently pending claims as required by In re Wilson. In addition, Applicants submit that the present subject matter is unexpectedly superior of the cited art.

Independent claim 41 is directed to a drug delivery system, comprising: a plurality of nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead, the nanoparticles or microparticle being in an amorphous, non-crystalline state which enhances dissolution of the poorly soluble drug upon administration; and a disintegrate mixed with the bead. Claims 42-44 and 50 depend either directly or indirectly from claim 41.

In contrast to the presently claimed subject matter, Desai et al. is directed to a protein coating of solid or liquid individual particles of the active agent(s). The protein

may also be used as the stabilizer of the emulsion droplet. *See* Desai et al. at the Abstract.

However, unlike the presently claimed subject matter, Desai et al. do not teach or suggest a drug delivery system, comprising: ***a plurality of nanoparticles or microparticles*** of a poorly soluble drug dispersed in a polymeric hydrophilic bead, ***the nanoparticles or microparticle being in an amorphous, non-crystalline state which enhances dissolution of the poorly soluble drug upon administration***; and a disintegrate mixed with the bead, as claimed.

Catron et al. do not remedy the deficiencies of Desai et al. Catron et al. is directed to a method for protecting the activity and bioavailability of heat and/or oxygen-labile compounds during processing of a food product containing the heat and/or oxygen-labile compounds. *See* Catron et al. at the abstract.

However, like Desai et al., Catron et al. do not teach or suggest a drug delivery system, comprising: ***a plurality of nanoparticles or microparticles*** of a poorly soluble drug dispersed in a polymeric hydrophilic bead, ***the nanoparticles or microparticle being in an amorphous, non-crystalline state which enhances dissolution of the poorly soluble drug upon administration***; and a disintegrate mixed with the bead, as claimed. Therefore, whether taken alone, or in combination, Desai et al. and Catron et al. do not teach or suggest every element of the claimed subject matter, as required under 35 USC § 103.

In addition, Applicants submit that the presently claimed subject matter exhibits unexpectedly superior results over the cited art. In particular, as described at the present specification at page 10:

> [i]t was surprisingly found that by performing the solvent evaporation process only after the beads are formed, the crystallization and increase in size of the drug molecule could be prevented.

Applicants note Example 4 shows that solvent evaporation before bead formation resulted in the formation of large crystals of the raw material indicating the instability of the drug nanoparticles.

Applicants submit that the presently claimed subject matter provides a drug delivery system with increased delivery of poorly soluble drugs. This is achieved by the formation of a polymeric hydrophilic bead, having dispersed therein, a plurality of microparticles or nanoparticles of the active agent and a disintegrate mixed with the bead.

The nanoparticles or microparticle are in an amorphous, non-crystalline state. The formation of the claimed drug delivery system is achieved by dissolving the poorly soluble drug in a volatile solvent so as to form nanoemulsions or microemulsions droplets, mixing the nano- or microemulsion with a water-soluble bead-forming hydrophilic polymer, and, after bead formation, evaporating the solvent. As evidence of this, Applicants respectfully draw the Examiners attention to the specification at page 12, which provides that:

> [u]pon further exposure to the crosslinking solution, the crosslinking ions migrate into the interior part of the bead, and form a solid matrix throughout the whole bead. ... Finally, as the last stage, the volatile (organic solvent) is evaporated together with the aqueous phase, ...to obtain the dry beads containing in their matrix dispersed nanoparticles of the poorly soluble drug.

In other words, the bead form a type of a large "cage" carrying a plurality of smaller particles.

The formation of a hydrophilic polymeric bead carrying a plurality of particles in an amorphous state provides the enhanced dissolution of the active agent upon administration, this being as compared to conventional drugs. In this regard, Applicants respectfully draw the Examiner's attention to the specification at of page 7, which provides that:

> ...the nanoparticles or microparticles are in an amorphous state, which increases their solubility rate, and subsequent crystallization is prevented....*See also* the specification at examples 10-13.

Applicants submit that neither Desai et al. nor Catron et al teach or suggest evaporation of the solvent from already formed beads. In this regard, Applicants submit that according to Desai et al., the coated droplets are formed by subjecting a mixture of the active agent and the stabilizing protein to high pressure and high shear forces for homogenization and emulsion formation. For example, at page 18, Desai et al. indicate that:

> The resulting emulsion comprises very small nanodroplets of the non-aqueous solvent (containing the dissolved pharmacologically active agent) and very small nanodroplets of the protein stabilizing agent. See Desai et al. at page 18, lines 27-30.

The mixture of droplets is then subjected to solvent evaporation whereby the coated particles are formed. According to Desai et al. at page 19, lines 18-20:

> [f]inally, the solvent is evaporated under reduced pressure to yield a colloidal system composed of protein coated nanoparticles of pharmaceutically active agent and protein.

In view of this, Applicants submit that Desai et al. is only enabling for formation of nanoparticles only if the stabilizer is a polymer. As shown in Example 4 of the present application, when using another type of stabilizer, large crystals are formed.

The presently claimed subject matter allows, on the other hand, the use of a broad spectrum of stabilizers (surfactants), which is not taught or suggested by Desai et al. or Catron et al.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination none of the cited references render the presently claimed subject matter obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VII. New Claim 65

Claim 65 has been newly added. As discussed, new claim 65 is directed to the "drug delivery system according to claim 41, wherein the poorly soluble drug is selected from the group consisting of simvastatine, statines, risperidone, carvedilol, carbamazepine, oxcarbazepine, zaleplon and galantamine."

Applicants respectfully submit that new claim 65 is both novel and non-obvious. Accordingly, Applicants respectfully request an indication that all of the pending claims are now allowable.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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